Genetic and environmental factors affecting birth size variation: a pooled individual-based analysis of secular trends and global geographical differences using 26 twin cohorts

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Abstract

Background: The genetic architecture of birth size may differ geographically and over time. We examined differences in the genetic and environmental contributions to birth weight, length, and ponderal index (PI) across geographic-cultural regions (Europe, North-America and Australia, and East-Asia) and across birth cohorts and how gestational age modifies these effects.

Methods: Data from 26 twin cohorts in 16 countries including 57613 monozygotic and dizygotic twin pairs were pooled. Genetic and environmental variations of birth size were estimated using genetic structural equation modeling.

Results: The variance of birth weight and length was predominantly explained by shared environmental factors, whereas the variance of PI was explained both by shared and unique environmental factors. Genetic variance contributing to birth size was small. Adjusting for gestational age decreased the proportions of shared environmental variance and increased the propositions of unique environmental variance. Genetic variance was similar in the geographic-cultural regions, but shared environmental variance was smaller in East-Asia than in Europe and North-America and Australia. The total variance and shared environmental variance of birth length and PI were greater from the birth cohort 1990-1999 onwards compared with the birth cohorts from 1970-1979 to 1980-1989.

Conclusion: The contribution of genetic factors to birth size is smaller than that of shared environmental factors, which is partly explained by gestational age. Shared environmental variances of birth length and PI were greater in the latest birth cohorts and differed also across geographic-cultural regions. Shared environmental factors are important when explaining differences in the variation of birth size globally and over time.

Keywords

birth weight, birth length, ponderal index, twins, genetics, pooled studies

Key messages

Additive genetic factors contributing to birth size have a small but consistent effect across geographic-cultural regions (Europe, North-America and Australia, and East-Asia) and across birth cohorts.

Environmental factors shared by co-twins importantly contribute to the inter-individual variation in birth weight, length and ponderal index, which is partly explained by gestational age.

Shared environmental influences were smaller in East-Asia than in Europe and North-America and Australia.

Introduction

Birth size is an indicator of infant health and is associated with health related traits in later life such as hypertension[1-3], obesity[4, 5], and psychosocial distress[6]. Moreover, low birth weight is associated with an increased risk of metabolic diseases including type 2 diabetes[7] and cardiovascular diseases in adulthood[8, 9]. Both genetic and environmental factors influence birth size[10, 11]. Associations between fetal genotype and birth weight can in part reflect the indirect effects of the maternal genotype influencing birth weight via the intrauterine environment[12]. Studying monozygotic (MZ) and dizygotic (DZ) twin pairs is a widely-used method to decompose total variance into fractions explained by genetic and environmental differences between individuals. The environmental factors shared by co-twins include gestational age, total placental weight, and maternal factors, such as maternal body size and smoking. Individual placental characteristics, such as placental function including nutrient capacity, anatomy, and perinatal injuries can lead to differences in birth size between co-twins and are thus part of the environment unique for each twin individual. A previous Dutch study found that the genetic factors explained almost an identical share of the total variation of birth weight and length when estimated by parent-offspring trios of singletons (26% and 26%, respectively) and MZ and DZ twins (29% and 27%, respectively), supporting the value of the twin design when studying birth size[13]. Gestational age affects birth weight and, because it is shared by co-twins, may lead to the overestimation of shared environment, if not accounted for[14].

Genetic and environmental variation of fetal growth may differ between populations because of differences in maternal dietary habits, other environmental exposures and the gene pool of population. A multinational twin study reported that genetic factors explained 17% of the variation of birth weight. This contribution was similar in Western and East-Asian populations, but there were differences in the proportions of environmental factors both shared and unshared by co-twins[15].

It is well known that maternal nutrition and other maternal factors affect birth size and the determinants of birth size may have changed across birth cohorts over the 20th century[16, 17]. However, there are no previous studies which would have analyzed how the role of genetic and environmental factors on birth size has changed over time. Further, the only international comparison was based only on seven twin cohorts[15]; larger studies would be warranted to get more precise estimates. Finally, it would be important to analyze also other indicators of birth size than birth weight, and gestational age should be adjusted for because otherwise the role of shared environment will be inflated. To address these questions, we used birth weight and length data available in the largest pooled database of twin cohorts in the world. We aimed to examine differences in genetic and environmental contributions to birth weight, length, and ponderal index (PI) (PI=weight (kg)/height (m^3)) across geographic-cultural regions (Europe, North-America and Australia, and East-Asia) and across birth cohorts from 1915 through 2013 and how gestational age modifies these effects.

Material and methods

Sample

The data were derived from the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins) database[18]. Information on birth weight was available in 26 cohorts from 16 countries, and birth length and gestational age were available in 14 and 17 of these cohorts, respectively. In the majority of cohorts, the birth-related measures were parentally reported (79% for birth weight, 87% for birth length, and 83% for gestational age) or self-reported (14%, 2%, and 8%, respectively) and only in a few cohorts, they were based on records from nurses or clinicians (7%, 11% and 9%, respectively). However, birth weights from maternal recall and medical records were found to be highly correlated[19]. The participating twin cohorts are listed in Table 1 (footnote) and were previously described in detail[18]. The prevalence of obesity and overweight is lowest in East-Asia, thus representing a less obesogenic environment, and highest in North-America and Australia, thus representing a more obesogenic environment[20]. Obesogenic environment can affect maternal dietary habits and maternal size, which indirectly reflect birth size[21-23]. Therefore, we divided these cohorts into three geographic–cultural regions: Europe, North-America and Australia, and East-Asia[20].

There were 121,997 twin individuals with data on birth weight. We excluded individuals with birth weight <0.5 or >5 kg (n=79) or without data on their co-twins (n= 6,606) as well as those with intra-pair difference in birth weight >2kg (22 pairs) or contrasting information on birth year between co-twins (21 pairs) leading to 57,613 twin pairs (38% MZ, 34% SSDZ and 28% OSDZ twins). For the analyses on birth length and PI, individuals without data on birth length (n= 64,626), those with birth length <25 or >60 cm (n=33), PI <12 or >38 kg/m^3 (n=675) or born before 1970 (n=261), and co-twins with intra-pair difference in birth length >12 cm (3 pairs) or PI >15 kg/ m^3 (9 pairs) were removed leading to 27,084 twin pairs (38% MZ, 33% SSDZ and 29% OSDZ twins).

We further standardized birth weight, length and PI for gestational age separately by sex and within the individuals included in each group of analyses. These three measures of birth size were expressed as SD scores of the respective means/weeks of gestation (z-scores; i.e., mean = 0 and SD = 1) to estimate their relative value for a given gestational age. Individuals with gestational age <25 or >45 weeks were excluded. Outlying values for birth weight, length and PI values for a given gestational age were checked by visual inspection of histograms for each gestational week and removed (0.2% for birth weight and 0.4% for birth length and PI) resulting in 38,806 (birth weight) and 23,742 twin pairs (birth length and PI) for analyses.

All participants were volunteers and gave their informed consent when participating in their original studies. A limited set of observational variables and anonymized data were delivered to the data management center at University of Helsinki. The pooled analysis was approved by the ethical committee of Department of Public Health, University of Helsinki.

Statistical analyses

The data were analyzed using genetic structural equations modeling[24]. MZ twins share virtually the same genomic sequence, whereas DZ twins share, on average, 50% of their genes identical-by-descent. On this basis, the total variance was decomposed into variance due to additive genetic factors (A: correlated 1.0 for MZ and 0.5 for DZ pairs), shared (common) environmental factors (C: by definition, correlated 1.0 for MZ and DZ pairs) and unique (non-shared) environmental factors (E: by definition, uncorrelated for MZ and DZ pairs). All genetic models were fitted by the OpenMx package (version 2.0.1) in the R statistical platform[25].

A full model with A, C, and E factors was fit to the data. We allowed a shared environmental correlation to be less than 1 for OSDZ pairs, as compared to 1 expected for SSDZ and MZ pairs; this would suggest the presence of sex-specific shared environmental factors affecting size at birth. Since boys and DZ twins showed greater birth size than girls and MZ twins, different means for sex and zygosity groups were allowed. We then conducted the analyses in the three geographic-cultural regions and across the birth cohorts from 1915 through 2013 per decade. Moreover, the genetic and environmental variances of birth weight were analyzed for each twin cohort. Birth weight, length and PI values (both unstandardized and standardized for gestational age) were first adjusted for twin cohort within each sex and geographic-cultural region/birth year groups using linear regressions, and the resulting residuals were used in the analyses.

Results

Birth weight was greater in European and North-American and Australian than in East-Asian newborns (Table 1). The variance of birth weight was greatest in North-America and Australia and lowest in East-Asia. Mean birth weight did not show any clear pattern across the birth cohorts until 1980-1989 but started to decrease from 1990-1999 onwards. Mean birth length in European and North-American and Australian boys and girls was greater than in East-Asians (Table 2). The variance showed a less clear pattern, but was greatest in European and lowest in East-Asian boys and girls. In MZ and DZ twins, the means of PI in boys were similar to those in girls in all geographic-cultural regions, except for East-Asia where MZ girls had the greatest PI. The mean PI of boys was similar between the geographic-cultural regions, whereas the mean PI of girls was greater in East-Asia than in Europe and North-America and Australia. The variances of PI were greatest in Europe and lowest in East-Asia in both sexes.

Figure 1 presents the additive genetic, shared environmental and unique environmental variances of birth weight, birth length and PI by the cultural-geographic region; the exact point estimates and their 95% confidence intervals (CI) are available in Supplemental table 1 and 2. Shared environmental factors explained the major part of the variation of birth weight and length whereas shared and unique environmental factors explained roughly equal shares of the variation of PI. When comparing the cultural-geographic regions, the differences in the variances were mainly explained by shared environmental variances. For birth weight, the shared environmental variance was lower in East-Asian boys (c^2=0.11, 95% CI 0.09-0.14) and girls (c^2=0.11, 95% CI 0.09-0.13) than found in Europe (c^2=0.19, 95% CI 0.18-0.20 and 0.18, 95% CI 0.17-0.18, respectively) or North-America and Australia (c^2=0.23, 95% CI 0.22-0.24 and 0.22, 95% CI 0.21-0.23, respectively). Similar differences in the shared environmental variances were also found for birth length and PI. When the results were adjusted for gestational age, especially the relative contribution of shared environmental variation to birth weight decreased. However, also in these analyses, the shared environmental variation was lower in East-Asia than in the other regions. For birth length and PI, the relative decrease in shared environmental variance after the adjustment of gestational age was smaller than for birth weight.

Figure 2 presents the corresponding results by birth cohorts (the exact point estimates and their 95% CIs are available in Supplemental table 1 and 2). For birth length and PI, the total variances were greater in the birth cohorts 1990-1999 onwards as compared with the birth cohorts from 1970-1979 to 1980-1989. Adjusting the results for gestational age decreased especially the proportions of shared environmental variance. After the adjustment for gestational age, systematic decrease in the shared environmental variance was found from the cohorts born in 1940-1949 (c^2=0.55, 95% CI 0.32-0.78 in boys and c^2=0.68, 95% CI 0.46-0.87 in girls) until 2000-2013 (c^2=0.17, 95% CI 0.10-0.26 and c^2=0.18, 95% CI 0.11-0.27, respectively).

Figure 3 presents the variances of birth weight in each twin cohort according to the cohort mean birth weight (the exact point estimates with their 95% CIs are available in Supplemental table 3). Some heterogeneity between the cohorts, especially in additive genetic variation, was found. However, this did not show any clear pattern according to the mean birth weight of cohort.

Discussion

Using data from 57,613 complete twin pairs from 16 countries, the present study revealed that environmental factors shared by co-twins importantly contribute to the inter-individual variation in birth weight, birth length, and PI. These factors also explained an important share of regional differences in the birth weight variation as found also in previous studies[11, 15, 26]. In the classical twin design, maternal effects shared by co-twins, including gestational age, would show up as a shared environmental variance. A previous international study of seven twin cohorts reported that from 50% to 70% of the total variance in birth weight was associated with maternal effects,[15] which is close to the relative contribution of shared environmental variance found in our study before standardizing the results for gestational age. The standardization for gestational age decreased especially the shared environmental variances for birth weight relative to the variances of birth length and PI suggesting that birth weight is more influenced by the length of gestation than birth length and PI[27].

The mean and total variance of birth weight and length were lower in East-Asia than in the other regions, which corresponds with previous studies[28, 29]. The differences in the total variances were especially contributed by differences in shared environmental variance. It has been suggested that part of these maternal effects is due to maternal genes which regulate fetal growth, possibly through intra uterine environment[30, 31]. Heritability estimates for the length of gestation were found over 30%[31, 32], indicating that it is a heritable trait in European ancestry populations. Heritability of the length of gestation for East-Asian populations is presently unknown, but if these differ from European ancestry estimates, this may partly explain these regional differences in shared environmental variances.

Various maternal genes have been shown to influence fetal growth, either directly or indirectly. A study examining genome-wide DNA methylation patterns in term human placentas showed that the patterns of DNA methylation were significantly associated with infant growth[33]. Moreover, a multi-ancestry genome-wide association study indicated that two loci (INS–IGF2 and RB1) of the 60 genome-wide significant loci from maternal sources fall within (or near) imprinted genes in fetal growth[12]. If the frequency of DNA methylation of gene and/or two loci among Asians differ from those among European ancestry[34], the genetic variability in maternal characteristics may explain some of the difference in shared environmental variance of birth weight between European ancestry and East-Asians detected in the present study.

Mean PI was similar among boys across the geographic-cultural regions. However, mean PI was greater in East-Asian than in European and North-American and Australian girls. Gilson et al. (2015)[27] indicated that PI varied between ethnicities. Moreover, in the present study, shared environmental variance differed between these regions. The smaller shared environmental variance observed in East-Asia than in the other regions may reflect differences in maternal nutrition, smoking, and other environmental factors.

The means and variances of birth weight and length were lower in the cohorts born after than before 1990. In the recent decades, the prevalence of preterm births among singletons and twins has increased in most industrialized countries, while at the same time perinatal mortality has decreased, mainly because of medically indicated preterm births[35-44]. Gielen et al. (2010) reported that the frequency of infertility treatment and caesarean sections as well as advanced maternal age have increased over the years, but none of these factors influenced the secular trends in birth weight[44]. The decrease in birth weight and length found in the present study may reflect the decrease in mean length of gestation up to 32 weeks as suggested by Gielen et al. (2010)[44]. Another factor with respect to time trends is the increasing survival of twin births. The survivors represent different proportions of the twin pregnancies[45], and these proportions might be represented differentially in the distributions of birth weight and birth length. We found evidence for these explanations since the results adjusted for gestational age did not show differences in the total variance of birth weight. This suggests that the increasing total variation over the birth cohorts is affected by increasing survival of babies with early gestational age. In the analyses adjusted for gestational age, shared environmental variance decreased over the birth cohorts. This may suggest that the variation in maternal factors has decreased at the same time when general standard of living has increased.

When considering how well our results can be generalized, the assumptions made by the twin design need to be considered. MZ twins can either share one chorion and one amnion, each fetus can have its own amnion, or they can each have their own chorion and amnion such for virtually all DZ twins. Previous Dutch and Belgian studies[46, 47] have reported somewhat lower correlations for mono-chorionic than di-chorionic MZ twins, which can lead to under estimation of additive genetic variance and over estimation of shared environmental variance. However, if there would be extra variation because of more dissimilar intrauterine environment of MZ twins, it should have been seen as the higher trait variance in MZ twins which was not the case in our study. One explanation is that very discordant pairs are not part of our study because of higher neonatal mortality or other reasons. It would be important to estimate the contributions of genetic and environmental factors also by using other methods available for singleton pregnancies to confirm how well our twin study results can be generalized to the whole population.

The main strength of our study is the very large sample size allowing the investigation of differences on the genetic and environmental contributions to individual differences in birth size in much more detailed than in previous studies. Pooling data from a large number of twin cohorts also permits the analyses by geographic-cultural regions and birth cohorts born over 100 years. Further, were able to analyze also birth length and PI and adjust the results for gestational age. Especially the lack of information of gestational age is a major limitation in previous studies since it inflates shared environmental variation as demonstrated in our study. However, countries and/or geographic-cultural regions are not equally represented, and the database is heavily weighted towards populations following the Westernized lifestyle. There are few data available from Middle-East and Africa and no data from South-Asia or South-America. It is also noteworthy that all countries have different historical development, and thus the same birth cohorts can have been exposed to different environmental exposures. This may well have diluted the differences between the birth cohorts in this study which reflects the average variances of different countries.

In conclusion, as contrast to the small contribution of genetic factors, environmental factors shared by co-twins importantly contribute to the inter-individual variation in birth size even after the standardization for gestational age. The contributions of genetic effects on birth size were similar in the geographic-cultural regions, but unique environmental influences were slightly larger and shared environmental influences smaller in East-Asia than in the other regions. This suggests that in the westernized social context there are features increasing variation in maternal nutrition and other maternal factors affecting birth size. Our results thus indicate that maternal factors importantly contribute to birth size and can then be a target for public health interventions to improve infant health.

Competing Interests statement

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Collaborators

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Table 1. Sample sizes, means and standard deviations of birth weight (kg) by sex, region, birth year, and zygosity

		Boys			Girls		
	Zygosity	N	Mean	SD	N	Mean	SD
	MZ	20596	2.52	0.55	22806	2412.5	529.1
All cohorts[1)]	DZ	36212	2.60	0.57	35612	2502.0	545.7
			Region				
Europe[2)]	MZ	13318	2.53	0.56	13974	2.42	0.53
Europe[2)]	DZ	24616	2.63	0.56	23598	2.52	0.54
NA and Aus[3)]	MZ	5258	2.52	0.56	6592	2.40	0.54
NA and Aus[3)]	DZ	9765	2.57	0.59	10223	2.47	0.57
East Asia[4)]	MZ	1910	2.48	0.51	2132	2.39	0.47
East Asia[4)]	DZ	1421	2.49	0.51	1403	2.41	0.47
			Birth year				
1915-1939	MZ	174	2.49	0.68	374	2.44	0.65
1915-1939	DZ	133	2.85	0.84	353	2.64	0.66
1940-1949	MZ	758	2.60	0.56	1280	2.47	0.52
1940-1949	DZ	1092	2.77	0.57	1558	2.61	0.51
1950-1959	MZ	1166	2.62	0.56	1952	2.46	0.54
1950-1959	DZ	1384	2.79	0.58	1900	2.66	0.56
1960-1969	MZ	286	2.63	0.58	480	2.40	0.55
1960-1969	DZ	176	2.72	0.64	284	2.53	0.59
1970-1979	MZ	3068	2.62	0.52	1826	2.48	0.48
1970-1979	DZ	3274	2.74	0.53	2048	2.63	0.51
1980-1989	MZ	2734	2.56	0.52	3072	2.49	0.52
1980-1989	DZ	3698	2.71	0.53	3722	2.61	0.52
1990-1999	MZ	8338	2.48	0.57	9474	2.38	0.53
1990-1999	DZ	16932	2.56	0.56	16634	2.47	0.54
2000-2013	MZ	4072	2.46	0.55	4348	2.36	0.52
2000-2013	DZ	9523	2.53	0.58	9113	2.43	0.55

1) Includes all cohorts in the footnotes 2-4 and Africa (one cohort, 108 twin pairs, Guinea-Bissau Twin Study) and Middle-East (one cohort, 400 pairs, Longitudinal Israeli Study of Twins)

2) Europe (11 cohorts, 37,753 twin pairs): East Flanders Prospective Twin Survey, Finntwin12, Finntwin16, Gemini Study, Hungarian Twin Registry, Italian Twin Registry, Norwegian Twin Registry, Swedish Young Male Twins Study of Adults, Swedish Young Male Twins Study of Children, Twins Early Developmental Study and Young Netherlands Twin Registry

3) North America and Australia (9 cohorts, 15,919 twin pairs): includes the following twin cohorts: Australian Twin Registry, Boston University Twin Project, Carolina African American Twin Study of Aging, Colorado Twin Registry, Michigan Twins Study, Minnesota Twin Family Study, Minnesota Twin Registry, Peri/Postnatal Epigenetic Twins Study and Quebec Newborn Twin Study

4) East-Asia (4 cohorts, 3433 twin pairs): Japanese Twin Cohort, Mongolian Twin Registry, Qingdao Twin Registry of Children and

West Japan Twins Registry

Table 2. Sample sizes, means and standard deviations of birth length (cm) and ponderal index (kg/m^3) by sex, region, birth year, and zygosity

		Birth Length						Ponderal Index					
		Boys			Girls			Boys			Girls		
	Zygosity	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
All cohort	MZ	10394	47.0	3.2	10054	46.4	3.3	10394	24.4	3.0	10054	24.3	3.3
	DZ	17758	47.5	3.3	15962	46.9	3.2	17758	24.4	3.1	15962	24.4	3.2
Region													
Europe[1)]	MZ	8614	47.1	3.3	8062	46.5	3.3	8614	24.4	3.1	8062	24.3	3.4
Europe[1)]	DZ	16040	47.6	3.3	14276	47.0	3.3	16040	24.4	3.2	14276	24.4	3.3
NA and Aus[2)]	MZ	350	47.0	3.3	348	46.6	2.8	350	24.3	2.8	348	23.9	2.8
NA and Aus[2)]	DZ	540	47.9	3.1	506	46.9	3.1	540	24.0	2.9	506	24.1	3.1
East- Asia[3)]	MZ	1418	46.4	2.8	1624	45.7	2.8	1418	24.2	2.5	1624	24.6	2.7
East-Asia[3)]	DZ	1096	46.2	2.9	1090	45.7	2.7	1096	24.5	2.6	1090	24.6	2.6
Birth Year													
1970-1979	MZ	2650	47.2	2.7	1300	46.5	2.5	2650	24.8	2.5	1300	25.0	2.7
1970-1979	DZ	2997	47.7	2.7	1785	47.1	2.5	2997	25.1	2.6	1785	25.2	2.7
1980-1989	MZ	1802	47.1	2.7	1936	46.5	2.9	1802	24.5	2.8	1936	24.8	2.9
1980-1989	DZ	2916	47.7	2.7	2862	47.0	2.7	2916	25.0	2.6	2862	25.1	2.8
1990-1999	MZ	4486	46.9	3.6	5160	46.3	3.5	4486	24.0	3.3	5160	24.0	3.4
1990-1999	DZ	8790	47.5	3.5	8422	46.9	3.4	8790	24.0	3.3	8422	24.0	3.4
2000-2013	MZ	1456	46.8	3.5	1658	46.1	3.5	1456	24.3	3.3	1658	24.1	3.4
2000-2013	DZ	3055	47.2	3.6	2893	46.5	3.4	3055	24.3	3.1	2893	24.3	3.3

1) Europe (11 cohorts, 23,496 twin pairs)
2) North America and Australia (9 cohorts, 872 twin pairs)
3) East-Asia (4 cohorts, 2614 twin pairs)

Figure legends

Figure 1. Additive genetic (grey), shared environmental (black) and unique environmental (white) variances of birth size measures before and after standardization for gestational age (GA) by geographic-cultural region.

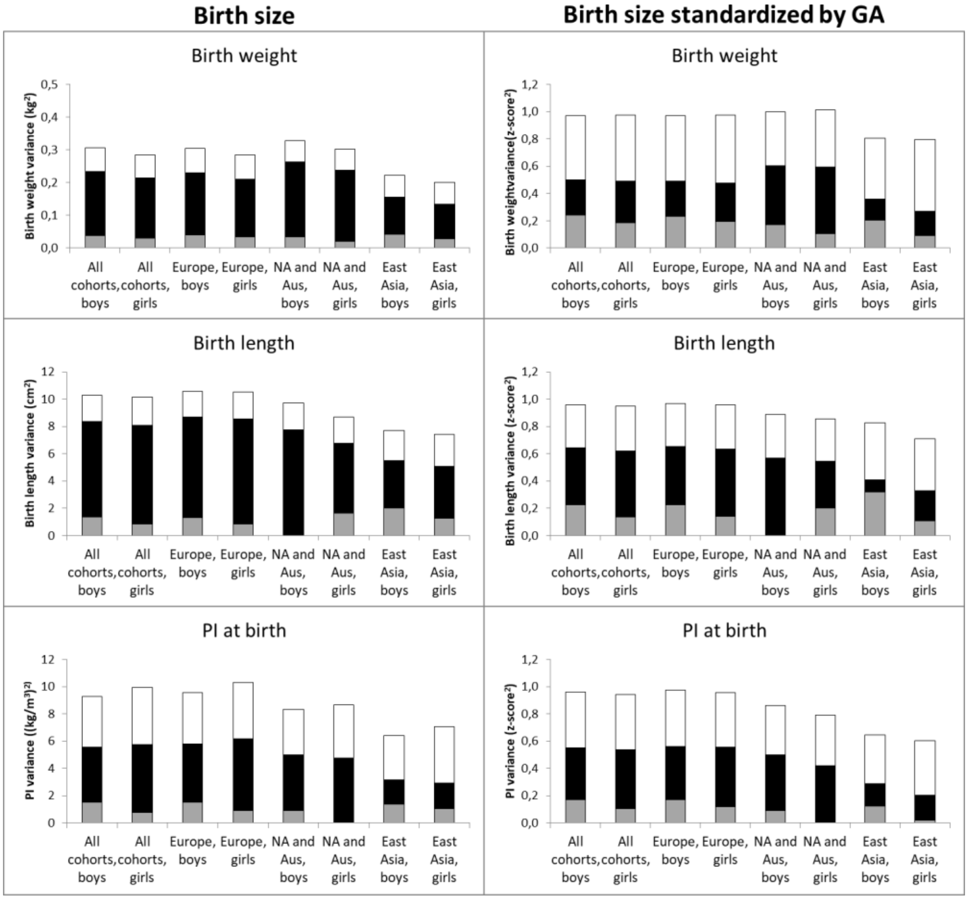

Figure 2. Additive genetic (grey), shared environmental (black) and unique environmental (white) variances of birth size measures before and after standardization for gestational age (GA) by birth cohort.

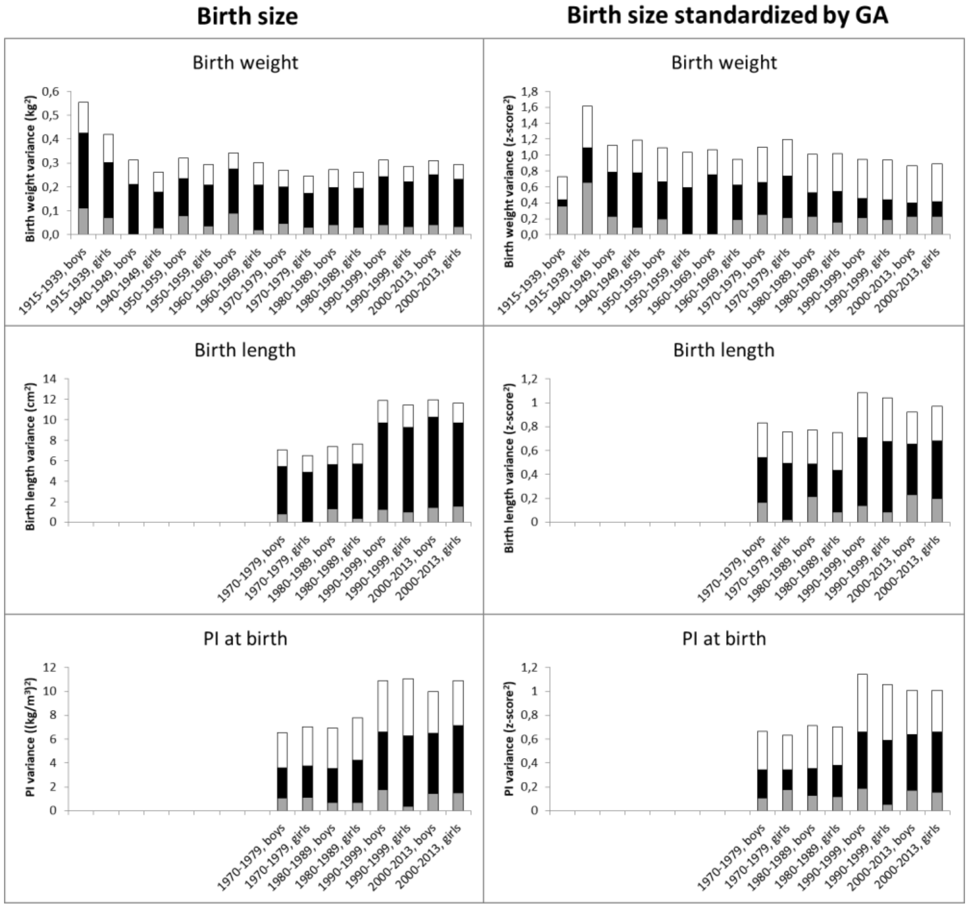

Figure 3. Total, additive genetic, shared environmental and unique environmental variances of birth weight by twin cohort. Au, Australian Twin Registry; Bo: Boston University Twin Project; Ca, Carolina African American Twin Study of Aging; Co, Colorado Twin Registry; EF, East Flanders Prospective Twin Survey; F12, Finntwin12; F16, Finntwin16; Ge, Gemini Study; GB, Guinea-Bissau Twin Study; Hu, Hungarian Twin Registry; It, Italian Twin Registry; Ja, Japanese Twin Cohort; Is, Longitudinal Israeli Study of Twins; Mi, Michigan Twins Study; MinC, Minnesota Twin Family Study; MinA, Minnesota Twin Registry; Mo, Mongolian Twin Registry; No, Norwegian Twin Registry; PETS, Peri/Postnatal Epigenetic Twins Study; Qi, Qingdao Twin Registry of Children; Qu, Quebec Newborn Twin Study; SwA, Swedish Young Male Twins Study of Adults; SwC, Swedish Young Male Twins Study of Children; TEDS, Twins Early Developmental Study; WJ, West Japan Twins and Higher Order Multiple Births Registry; Ne, Young Netherlands Twin Registry.